



Aegle marmelos: A Golden Apple of Health with Multifaceted Therapeutic Properties

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ABSTRACT

One plant with considerable therapeutic promise is the bilva tree, *Aegle marmelos*. This overview summarizes current scientific research on the plant's several parts, including as the leaves, fruits, bark, and roots, as well as traditional knowledge. Its varied pharmacological actions are caused by its rich phytochemical profile, which consists of flavonoids, coumarins, alkaloids, and essential oils.

Based on research on both humans and animals, the review emphasizes the plant's anti-proliferative, neuroprotective, hypoglycemic, and anti-diarrheal qualities. Certain substances, such as imperatorin and aegeline, have demonstrated promise in the treatment of epilepsy and Parkinson's disease. Studies have shown that the plant has strong antiviral, antibacterial, and antioxidant properties. It also helps to neutralize free radicals and is effective against a variety of infections. Additionally, studies have looked at its analgesic, anti-inflammatory, and anti-spermatogenic properties, indicating that it may be used for male contraceptive, pain relief, and inflammation control. This thorough analysis highlights *Aegle marmelos*' medicinal benefits as well as its room for additional study and advancement in contemporary medicine.

KEY WORDS

Bilva, *Aegle marmelos*, bael, Pharmacological study, ethnobotanical uses, phytochemicals

INTRODUCTION

The use of plants or plant parts as sustenance marked the beginning of the journey of life for humans, animals, and birds. Different plant parts, such as the root, stem, leaf, and flower and fruits are necessary for the animal kingdom to survive. Of all the species that now inhabit the planet, humans are thought to be the most advanced. Since ancient times, they have been using plants to treat a variety of human illnesses in addition to using them as a source of sustenance. Numerous plants or plant parts are utilized to treat a variety of mental and physical illnesses and to help us cope. Plants can be used to treat a variety of health issues, according to ancient texts like the Rigveda, Yajurveda, Atharvaveda, Charak Samhita, and Sushrut Samhita.¹

Despite its continued underutilization in conventional agriculture, bilva is a rich botanical resource due to its tolerance to a variety of soil types and climates (Wiley Online Library). The IUCN Red List's designation of it as "Near Threatened" emphasizes how crucial conservation is.

Traditionally, various parts of the bilva tree—including its leaves, fruits, bark, and roots—have been utilized to treat a spectrum of ailments such as gastrointestinal disorders, respiratory issues, and metabolic conditions. Modern phytochemical analyses have identified a rich composition of bioactive compounds in *A. marmelos*, including alkaloids, coumarins, flavonoids, and essential oils. These constituents contribute to its diverse pharmacological properties, which encompass anti-diarrhoeal, antimicrobial, antiviral, anticancer, antidiabetic, anti-inflammatory, and antioxidant activities.

The leaves, fruits, bark, and roots of the bilva tree have all been used traditionally to cure a variety of illnesses, including respiratory, metabolic, and gastrointestinal disorders. Alkaloids, coumarins, flavonoids, and essential oils are among the many bioactive substances found in *A. marmelos*, according to contemporary phytochemical investigations. Its various pharmacological characteristics, including antidiarrheal, antibacterial, antiviral, anticancer, antidiabetic, anti-inflammatory, and antioxidant effects, are facilitated by these ingredients².

TABLE NO.1-TAXONOMY- table no.1³

Taxonomical rank	classification
kingdom	Plantae
subkingdom	Tracheobionta
Super-division	Spermatophyta
division	Magnoliophyta
class	Magnoliopsida
subclass	Rosidae
order	Sapindales
family	Rutaceae
Genus	Aegle
species	Aegle marmelos

TABLE NO.2- VERNACULAR NAMES OF AEGLE MARMELOS¹

Latin	Aegle marmelos
Indonesian	Mojo tree
Bengali	Bel, Shreefal
Malay	Pokok Maja Batu
Marathi	Kaveeth
Nepali	Bel, Gudu
French	Oranger du Malabar
Urdu	Bel
Thai	Mapin, Matum, Tum
Vietnamese	Mbau Nau, Trai Mam
English	Wood/Stone apple, Bengal Quince, Indian Quince
Old Hindi	Sir Phal
Sanskrit	Shreephala, Bilva, Bilwa
Tamil	Vilva Maram, Vilva Pazham
Javanese	Modjo
Khmer	Banu
Lao (Sino-Tibetan)	Toum
Telugu	Maredu
Portuguese	marmelos
Cambodia	Phneou or pnoi
Gujrati	Bil

DISTRIBUTION

A. marmelos is a subtropical plant that may reach elevations of 1,200 meters above sea level. It thrives in arid woodlands on plains and hillsides. *A. marmelos* is a plant that grows worldwide and can be found in the following countries: Bangladesh, Nepal, India, Ceylon, China, Myanmar, Pakistan, Laos, Cambodia, Thailand, Indonesia, Malaysia, Tibet, Sri Lanka, Java, the Philippines, and Fiji. It is found in central and southern India's Sub-Himalayan regions, extending from Jhelum east to West Bengal. It is present in practically every Indian state.⁴

MORPHOLOGY

A marmelos is a small deciduous tree with a trunk diameter of 25–50 cm and a height of 10-15 m. The elder branches have single or paired spines that are 1-2 cm long.

LEAVES

The color of the leaves is different in different phase of the leaves; it is very green and fresh to see in the early stages, but later on it looks like dark green in color.⁵ The petiole is 2-4 cm long, and the leaves are trifoliate and placed alternately. The terminal petiolules can reach a length of 15 mm, while the lateral ones can reach up to 3 mm. The terminal leaflets are obovate, up to 7.5 cm x 4.8 cm, and densely minutely glandular-punctate, whilst the lateral leaflets are oblong to elliptic, up to 7 cm x 4.2 cm.



FLOWER

The axillary racemes that make up the inflorescences are crowded and 4-5 cm long. The sepals are 1.5 mm long and widely deltoid. The petals are 14 mm by 8 mm, oblong-obovate, and greenish to white in color. There are 4-7 mm long filaments and 35-45 white stamens. The ovary has a very short style and measures 8 mm by 4 mm. The flower of *A. marmelos* has a lovely scent and is hypogynous and bisexual in character. Some lateral panicles, which are supported by the leaf axil, hold the greenish- white bael flowers jointly⁶

FRUIT

The fruit is a spherical berry that ranges in diameter from 5 to 12.5% and frequently has a stiff, woody shell. Its segments number 8-16(-20), and its clear, sticky, and tasty pulp. The fruit pulp can range in hue from vivid orange to sunset yellow, and it contains 6-10 seeds that are encased in thick, transparent mucilage and have grooves. In addition to having many seeds, it has some dots on the outside. When the fruit is immature, it is greenish; when it ripens, it becomes yellowish. The therapeutic properties of both ripe and unripe fruits are utilized⁷



SEED

Each woolly-hairy seed has a white testa and is encased in a sac of sticky mucilage that solidifies when it dries.

**BARK**

When the tree's bark is examined, it is discovered to be thick in nature. Gum secretion is also seen after the bark is gently thrashed, and the thickness increases when air is present.⁸

**PHYTOCHEMICAL**

Aegle marmelos's extensive phytochemical profile is thought to be responsible for its medicinal potential. Numerous bioactive substances, such as alkaloids, coumarins, flavonoids, tannins, terpenoids, and phenolic compounds, have been shown to be present in the plant's leaves, fruit, root, and bark. Notably, coumarins such as marmesin, imperatorin, and scopoletin, as well as alkaloids like aegeline, marmeline, and aegelenine, have been isolated from different plant sections. Numerous biological actions, including anti-inflammatory, antibacterial, antidiabetic, and antioxidant properties, are displayed by these phytochemicals⁹. According to recent research, the root and leaf extracts include unique cinnamide compounds and prenylated flavonoids, which may have use in medication development in the future¹⁰

BIOACTIVE SUBSTANCES	ISOLATED CHEM. COMPOUND	REFERENCES
TERPINOIDS	p-Menth-1-en-3,5-diol	11
	α -Phellandrene, β -Myrcene, Iso-sylvestrene, β -Ocimene	12
	p-cymene	13
	Limonene	14
	α -Pinene	15
VITAMINE	Thiamin, Riboflavin, Niacin, Ascorbic Acid	13
ALKALOIDS	marmeline	16
	O-3,3-(dimethylallyl)halfordinol	17
	N-2-ethoxy-2-(4-methoxyphenyl) ethylcinnamamide, Aegelinosides B	18
	N-2-methoxy-2-(4-methoxyphenyl) ethylcinnamamide	19
	Anhydromarmeline	20
	Aegelinosides A	21
COUMARINES	Marmelosin	22
CARBOHYDRATE	Marmesin, Imperatorin, Alloimperatorin, Scopoletin, Marmin, Scoparon, Xanthotoxol, Marmelide, Methyl ether, Psoralen, Umbelliferon	20
	Umbelliferon	20
	Galactose	23
	L-rhamnose	24
	Arabinose	21
	Uronic acid	22
TANNIN	Carotene	25
	Umbelliferon, D-galacturonic Acid, Allo-imperatorin, Auraptine, Marmin, Psoralin, Xanthotoxin, Scopoletin, Marmesin, Luvangetin, Lupeol, Alpha- amyrin, Skimmlamin, Lembamide, Dimethoxy Coumarin, Aralrinose, Imperatorin	23
FLAVONOIDS	4,7,8-trimethoxyfuro-quinoline	26
ESSENTIAL OIL	Flavone glycosides	27
	Flavone-3-ols, Rutin, Flavone	26
FATTY ACIDS	Delta-Carene 38	28
	Isosylvestrone, Beta-Ocimene, Linalool, 4-Terpineol, Alpha-Pinene, Alpha- Terpineol, Alpha-Cubebene, Alpha- Phellandrene, Delta-Elemene, Beta- Myrcene, Trans-2-hydroxy cinnamic acid, 3-Isothujanol, Thuj-3-en-10-al, Terpenolene, Alpha-Humulene, Gama- Terpinene, Alpha-Terpinyl isobutyrate, Gama-Elemene, Valencene, Beta- Selinene, Gama-Curcumene, Beta- Bisabolol, Beta-Bisabolene, Gama- Cadinene, Alpha-Murolene	27
FURANOCOUMARIN	Heraclenin	30
PSORALENS	Methoxsalen	27
SESQUITERPENE	Germacrene B, Alpha-Guaiene, Caryophyllene	27

Ethnic value of *Aegle marmelos*

There are 68 million people in India, who are divided among 227 ethnic groups (573 tribes communities)²⁹, reside adjacent to villages or forests and have been successful in preserving the ecology of their areas. Their livelihood and traditional medicines are supported by the forest and its trees and plants, in addition to their everyday needs for fuel wood and lumber. There are 45,000 species of wild plants, of which 7500 are used in herbal and therapeutic applications and 9500 are significant to ethnobotany³⁰. Because they are thought to be the homes of God and Goddess³, many of these plants are protected and revered in their natural environments. Among them is Bael, who is revered as a representation of Lord Shiva. Sacred groves are home to many of these floras. According to estimates, the total number of holy groves in the The nation is home to 100,000–150,000¹⁴ people³¹. These are mostly found in the Andhra Pradesh, Bihar, Jharkhand, Orissa, and Maharashtra³² states. 15. According to an ancient custom known as "Sacred Groves," a section of woodland or body of water is devoted to regional deities, and no one is permitted to chop down vegetation, kill animals, or harm any other living thing there. Sacred groves have existed since the pre-agrarian hunting-gathering era of human civilization and are known to flourish across the majority of India. One of the key plants in these Jharkhand⁶ sacred groves is *A. marmelos*. Sacred groves serve as a vital life support system in addition to being significant for biodiversity protection. The hallowed groves Additionally, it purifies the atmosphere by sinking air contaminants and deodorizing odorous air³³. A sacred grove in Panchmarhi hamlet, where the Gonds worship *A. marmelos* in addition to other sacred trees, serves as an illustration of a sacred grove.

PHARMACOLOGICAL ACTIVITY

Anti-proliferative / Anticancer (Animal + cell models)

- **Animal study:** In DMBA- induced mammary tumors in Charles Foster rats, oral ethanolic fruit pulp extract at 200 mg/kg/day for 5 weeks significantly reduced tumor volume, decreased serum TNF- α , MDA, and glucose levels, and improved liver/kidney³⁴
- The cells' viability dropped from 100% to 50%. Following the extract's administration, MMP-2 and MMP-9 mRNA expression dropped. We may infer from this study that *Aegle marmelos*, a new and creative anticancer medication, has anti-cancer properties and reduced the growth of liver cancer cells by lowering the production of MMP 2 and MMP 9³⁵.
- The hydroalcoholic extract of *A. marmelos* exhibits strong antitumor and antioxidant activities in DLA-bearing mice³⁶.

Neuroprotective / Anti- amyloidogenic (Human cell- line)

- **In vitro human SH- SY5Y neuroblastoma model:** Ethanolic fruit extract protected cells from A β 1- 42 induced toxicity, improved viability, reduced ROS, restored mitochondrial membrane potential, and inhibited amyloid- β aggregation; also showed AChE inhibition³⁷
- Implications for Alzheimer's Disease Treatment: According to the findings, *A. marmelo*'s ethyl acetate fraction is a substantial source of polyphenolic chemicals that may have antioxidant and AChE-inhibiting properties, making it a promising therapy option for Alzheimer's Disease³⁸.
- Implication in Parkinson disease-Derf and associates. Aegeline, a chemical ingredient extracted from AM leaves, is highlighted in the 2019 study along with its effect on a mechanism. Aegeline was discovered to suppress SNARE protein ySec22p activity, which in turn suppresses apoptosis in yeast-induced Parkinson's disease by both Bax and α -syn. In Parkinson's disease, these two human proteins are essential for neuronal death. The experimental results are validated by molecular modeling. Aegeline shows promise as a treatment for Parkinson's disease, according to the yeast-based experiment³⁹.
- An isolated chemical component from AM called imperatorin (coumarin derivative) has been shown to have antiepileptic properties in animal models, demonstrating that AME therapy can lessen the severity of seizures brought on by PTZ and MES. This protective effect may result from PPAR-c activation, which further inhibits NO production. Chronic AME treatment can lower postictal depression in mice. Hypoglycaemic / Antidiabetic (Animal + small human)
- **Animal models:** In alloxan- induced diabetic rats and rabbits, aqueous/alcoholic extracts (approx 400–500 mg/kg) significantly lowered fasting blood glucose in male albino rats and rabbits³³
- **Human (type 2 diabetes supplementation):** Leaf juice (20 g/100 ml) daily for 60 days improved biochemical

parameters in T2DM patients.⁴⁰

- With an IC₅₀ of 3.36 µg/ml, a fruit lectin extract was more effective than the common drug metformin at promoting yeast cells' absorption of glucose. Because of its high level of active ingredients and antioxidant activity, this study indicated that the fruit extract from *A. marmelos* has hypoglycemic activity⁴¹.

Antidiarrheal / Gastroprotective / Anti-ulcer (Animal)

- **Animal studies in rats:** Unripe fruit methanolic/aqueous extracts reduced diarrhea by decreasing gut motility and secretions; seed extract and ripe fruit inhibited NSAID- and *H. pylori*- LPS-induced gastric ulcers by enhancing mucus, prostaglandin, and mucosal defense; quercetin and lupeol implicated⁴².
- Using ranitidine as a reference (50 mg/kg), methanolic and aqueous extracts of *A. marmelos* seeds were evaluated for antiulcer action in ulcers caused by indomethacin, stress, and pylorus ligation⁴³.
- In Ayurveda, *A. marmelos* is commonly used to treat ulcers and associated conditions. Oral treatment of *A. marmelos* methanolic extract has been shown to help rats with stomach ulcers brought on by *Helicobacter pylori*-induced lipopolysaccharide⁴⁴.

Antioxidant Activity (In vitro and Animal)

- **Studies:** Extracts from fruit, leaves, and seeds show strong DPPH, FRAP, nitric oxide, superoxide scavenging in vitro; in animal studies improve antioxidant enzyme activities (SOD, catalase, glutathione) and reduce lipid peroxidation⁴⁵
- Antioxidants are organic complexes that can safely interplay with free radicals and stop the chain reaction before harming fundamental molecules. Free radicals are highly reactive molecular species containing one or more unpaired electrons. They are generated from regular metabolism while using O₂ to burn food for energy⁴⁶
- Reactive oxygen species (ROS) are recognized to contribute to the development of a number of diseases, such as cardiovascular disease and cancer. Antioxidants or polyphenols found in plants can effectively neutralize these ROS and stop the spread of illness⁴⁷.

Antimicrobial & Antiviral (In vitro)

- **In vitro:** Aqueous, ethanol and essential-oil extracts from leaves, fruit and bark show antimicrobial activity against *E. coli*, *Salmonella typhi*, *Staphylococcus aureus*, *Klebsiella*, *Candida*, *Vibrio*, and efficacy against dengue virus and herpes viruses⁴⁸.
- Using ribavirin, a common antiviral medication, several parts of *A. marmelos* have been shown to exhibit in-vitro antiviral activity against human coxsackie viruses B1–B6. Marmelide therefore has 32 times the inhibitory action of ribavirin⁴⁹.
- *A. marmelos* extracts were shown to be effective against the white spot syndrome virus in shrimp at a dose of 150 mg/kg of animal body weight⁵⁰
- The ability of the extracted volatile oil from *A. marmelos* to stop the growth of eight different kinds of fungi is investigated. The essential oil totally stopped all fungi from making spores at a dosage of 0.05%. About 75% and 90% of the fungus is considerably suppressed at 0.03% and 0.04%, respectively. The most resistant strain, *F. udum*, demonstrated 65% and 80% inhibition rates at doses of 0.03% and 0.04% of the oil, respectively⁵¹.

Anti-inflammatory & Analgesic (Animal)

- **Animal studies:** Methanolic extracts of leaves and flowers reduce carrageenan-induced paw edema in rats. Fruit extracts also reduce colitis inflammation and tumor-associated inflammatory markers like TNF- α in rodent models⁵².
- The study looked at the repeated extracts from *A. marmelos* leaves' possible anti-inflammatory properties. The antipyretic and analgesic properties of the leaf extracts were established by showing an apparent analgesic effect in mouse models of cotton-pellet granuloma and carrageenan-induced paw edema. Additionally, the early and late phases of paw licking were diminished, and hyperpyrexia decreased⁵³
- Wistar rats are used to test the aqueous extract of dried flowers from *A. marmelos* for its anti-inflammatory qualities. Two hours after delivery, 200 mg/kg of water extract had the strongest anti-inflammatory effects⁵⁴.

Antispermato-genic activity

- Sperm locomotor activity was found to be positively impacted by the ethanolic extract of *A. marmelos* bark.

Additionally, it has been noted that sperm motility is decreased when extract concentration is increased. Male albino rats' fertility was considerably reduced by the alkaloids extracted from *A. marmelos* leaves in a dose-dependent manner⁵⁵.

- Because it can totally suppress pregnancy and quickly restore fertility after therapy ends, *A. marmelos* extract is a great option for male contraception⁵⁶.
- The male albino rats reproductive systems were subjected to three various doses of a 50% ethanolic extract from *A. marmelos* leaves: 100, 200, and 300 mg/kg 1 day 1 for each rat for 60 days. All of the significant accessory sex organs shrunk after ingesting the extract⁵⁷.

ANTIMALERIAL ACTIVITY

- *marmelos* at 20 and 40 mg/kg body weight suppressed parasite infection, while *C. longa* therapy did not affect infected mice with a suppressive impact on the parasite. Last but not least, *A. marmelos* showed potent antiplasmodial and antioxidant qualities; it may be one of the traditional plants used to cure malaria⁵⁸.
- *A. marmelos* leaf methanol extract demonstrated the strongest antimalarial efficacy against *Plasmodium falciparum* in vitro, with minimal cytotoxicity. Its potential antiplasmodial activity, with an IC₅₀ of 7 g/ml, was also observed⁵⁹.

ANTIARTHRITIC ACTIVITY

- It has been shown that *A. marmelos* leaves have antiarthritic properties against collagen- induced arthritis in Wistar rats. Rats treated with methanol extract demonstrated less paw edema. and the index of arthritis. Rats given methanol extract also showed a significant decrease in radiological and histological alterations⁶⁰.

RADIOPROTECTIVE ACTIVITY

- One of the most significant cancer treatments available today is radiation therapy, especially for patients with critical gastrointestinal cancers. This medication is routinely curing a significant number of cancer patients worldwide. But there are some negative consequences of the radiation as well. The radioprotective potential of bilva fruit hydroalcoholic extract has also been investigated in mice exposed to varying gamma radiation dosages. It has been discovered that giving the extract (20 mg/kg) intraperitoneally for five days in a row before to gamma ray irradiation provides the most protection, as shown by the largest number of survivors 30 days following radiation^{61,62}.

TOXICITY OF *aegle marmelos*

Fruit is typically used as a nourishing food, and *A. marmelos* is used extensively in traditional medicine. However, because *A. marmelos* leaves have historically been used to induce abortion and sterilize, it is not advised for pregnant or nursing women to consume *A. marmelos*. The acute and subacute toxicity characteristics of *A. marmelos* leaves have recently been investigated. Wistar albino rats were used to test the various extracts of *A. marmelos* leaves for LD₅₀ values as well as acute and subacute toxicity effects. The findings showed that the various extracts' LD₅₀ values ranged from 1300 mg to 1700 mg/kg body weight. Dead animals typically presented with their hearts in a systolic stand still during acute poisoning⁶³.

The histological investigations showed no appreciable alterations following 50 mg/kg body weight (daily 14 days). The topological profile of *A. marmelos*'s dried fruit pulp was examined. extract of *A. ethanol*.

Swiss albino mice were used to investigate for acute oral toxicity of *marmelos* dried fruit pulp at 550 and 1250 mg/kg body weight. The test extract did not exhibit any toxicity at these doses. Throughout the 14-day experiment, mice's behavior and physiological activities did not change. According to the findings, the test extract's LD₅₀ is greater than 1250 mg/kg body weight⁶⁴.

CONCLUSION

The comprehensive review of *Aegle marmelos* reveals its profound therapeutic significance, bridging the gap between its historical use in traditional medicine and its validation through modern scientific research. The plant's rich and diverse phytochemical profile, including alkaloids, coumarins, flavonoids, and essential oils, is the foundation for its wide range of pharmacological activities.

Scientific studies have robustly demonstrated its efficacy as an anticancer, neuroprotective, antidiabetic, and anti-diarrheal agent, among other properties. Specific compounds like aegeline and imperatorin have shown promising results in treating complex neurological disorders such as Parkinson's and epilepsy. Furthermore, the potent antioxidant, antimicrobial, and antiviral capabilities of *Aegle marmelos* highlight its potential as a natural defense against various pathogens and oxidative stress-related diseases. The plant's use extends to reproductive health, with studies confirming its anti-spermatogenic effects, suggesting its potential for male contraception.

In summary, *Aegle marmelos* is more than just a traditional medicinal plant; it is a valuable natural resource with a validated pharmacological profile. Despite the wealth of research, further studies are warranted to explore the full therapeutic potential of its individual compounds, determine clinical dosages, and develop standardized herbal

formulations. This ongoing research will pave the way for its integration into modern medicine, ensuring that the ancient wisdom surrounding this remarkable plant continues to benefit future generations.

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